IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Donoho *et al.*	Group Art Unit: 1653	
Application No.:	09/691,344	Examiner: R. Mitra	
Filed:	10/18/00		
Title:	Novel Human Proteins and Polynucleotides Encoding the Same	Atty. Docket No.:	LEX-0071-USA

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED MAY 6, 2003

Commissioner for Patents
Alexandria, VA 22313

Sir:

Applicants acknowledge the receipt of the Office Action ("the Action") mailed on May 6, 2003 (Paper No. 15), which has been carefully reviewed and studied. The Examiner is respectfully requested to reexamine and reconsideration of the application in view of the following remarks. In order to facilitate the Examiner's evaluation of the application, Applicants have attempted to address the objections and rejections in Paper No. 15 in the same order in which they were originally raised.

A Petition for an Extension of Time of two months to and including October 6, 2003 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Applicants' representatives Deposit Account are included. The response is thus timely filed. Applicants believe no fees in addition to the fee for the extension of time are due in connection with this response. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0892.

RESPONSE

I. Status of the Claims

Claims 1-3, 6 and 7 are therefore presently pending in the case.

II. Rejection of Claims 1-3, 6 and 7 Under 35 U.S.C. § 101

The Action includes a new ground for rejection of claims 1-3, 6 and 7 under 35 U.S.C. § 101 because allegedly the specification does not provide either a specific or substantial asserted utility or a well-established utility, and thus, does not support the claimed invention.

The Action notes that the sequences of the present invention have a high degree of homology with a human Tango cDNA and the protein it encodes. However, the publication in which the Tango molecule was named and identified by Mackay *et al.*, (AAU00670) is a pending PCT patent application. Therefore, the identification of the sequences of the present invention as encoding a "Tango" protein is no more valid than Applicants identification of these sequences as encoding CUB domain containing proteins. In fact Applicants identification of the sequences of the present invention as CUB domain containing proteins provides structural/functional information that the assigned name Tango protein does not.

Furthermore, Applicants respectfully invite the Examiner's attention to the fact that a sequence sharing greater than 99% identity at the nucleic acid level over the entire length of SEQ ID NO:1 (and over large regions of SEQ ID NOS: 3, 5 and 7 as well) of the present invention is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Appellants* as Homo Sapiens discoidin, CUB and LCCL domain containign (DCBLD1)(GenBank accession number NM_173674; GenBank report and alignment with SEQ ID NO:1 provided in **Exhibit A**, alignments with SEQ ID NOS: 3, 5 and 7provided as **Exhibit B**). Thus, the present case is similar to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), wherein a sequence bearing a high degree of homology to a known sequence is recognized as having patentable utility. Thus clearly those of skill in the art would recognize that Applicants assertions that the sequences of the present invention encode a CUB domain containing protein are credibleGiven the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible

or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Action also takes the position that one can not assign biological activity based on bioinformatic informatio and cites an article that states that "A protein's amino acid sequence is not sufficient to determine its biological activity." (Y.Bidault, The next generation of bioinformatics software: Examining proteins on the desktop computer," American Biotechnology Laboratory, January 2002). In fact, this article does not support this position as it is a promotional publication by the Marketing Manager of software designed for the desktop computer that uses amino acid sequence to determine a protein's 3D structure, which the author considers to be a more accurate predictor of protein function. The major difficulty with the position taken in this publication is that the 3D structure is determined in large part by the amino acid sequence. Therefore to take the position that "A protein's amino acid sequence is not sufficient to determine its biological activity", is to also take the position that the very basis of your 3D structural determinations is without validity. Obviously, this is not the intended argument that the Marketing Manager of such a software program wishes to put forward.

Furthermore, this is just one of the few spurious articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. Appellants agree that there is not 100% consensus within the scientific community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants respectfully point out that the lack of 100% consensus on prediction of protein function from homology information is irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is **not the standard** for patentability under 35 U.S.C. § 101. Appellants respectfully point out that, as discussed

above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools, as evidenced by extensive number of journal articles (which support Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatic predictions), and would thus **believe** that Appellants sequence is a CUB domain containing protein. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus or 100% accuracy, Appellants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

Applicants' respectfully submit that the sequences of the present invention can be used on DNA chips an application that meets the requirements of § 101. The Action suggests that as Applicants must identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications, particularly as the specification teaches specific tissues which express these sequences. The claimed sequence provides

a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Furthermore, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of

much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit C**. This is the result of a blast analysis using SEQ ID NO: 1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 13 exons spread non-contiguously along a region of human chromosome 6q21, which is contained within BAC clone Z85999.1. Thus clearly one would not simply be able to identify the 13 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

Finally, Applicants submit that there is an issue of due process presented in previous response is not persuasive. Applicants understanding is that issued United States patents retain a legal

presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 1-5 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

III. Rejection of Claims 1-3, 6 and 7 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3, 6 and 7 under 35 U.S.C. § 112, first paragraph, since the claimed invention is not supported by either a specific or substantial or well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention, so that it would operate as intended, without undue experimentation. However, as it has been clearly demonstrated above that the claimed invention is supported by specific and substantial utilities, this rejection has been avoided and Applicants respectfully request withdrawal of the rejection.

The Action also maintains rejection of Claim 3 allegedly due to the belief that Claim 3 is

indefinite for reciting the term "cDNA" which is said to be inherent in Claim 1. Applicants respectfully submit that there are those who would define a cDNA strictly as that which is derived by reverse transcription from RNA only. Thus while an cDNA is an isolated nucleic acid not all isolated nucleic acids are cDNAs. For example, RNA is an isolated nucleic acid that is not cDNA. Therefore, under such a definition, Claim 3 does further limit Claim 1.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Mitra have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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Date

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